Maternal sensitivity and mother-infant attachment are associated with antibiotic uptake in infancy

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ABSTRACT

Attachment security has been associated with health status and symptom reporting. In this longitudinal study, we investigated the association between antibiotics uptake by infants at 9-months and mother-infant attachment at 12-months. Logistic regression analyses indicated that lower maternal sensitivity was associated with increased odds of antibiotic uptake. Furthermore, 89.7% of insecure-ambivalent infants consumed antibiotics, which contrasted with 32.5% of avoidant infants and 21.5% of secure infants. This study suggests that maternal behavior and mother-infant attachment impact on antibiotic consumption, which is worrying because antibiotics may lead to several health problems later in life and antibiotic-resistance.

INTRODUCTION

Symptom-reporting has been shown to affect the propensity of antibiotic prescription by general health practitioners (Sirota, Round, Samaranayaka, & Kostopoulou, 2017). It is well documented that medical doctors are often under pressure to prescribe antibiotics, even when these drugs are unnecessary or unhelpful (for example, in the case of diseases caused by viruses). Several factors contributing to this problem have been identified, namely patients' lack of knowledge and concern (Altiner et al., 2007), underestimation of antibiotic resistance (Wood et al., 2013), and patients' coercion over medical doctors to prescribe antibiotics (Arroll, Kenealy, & Kerse, 2003). Additionally, antibiotic prescription encourages patients to assume the use of antibiotic treatment in future episodes of illness (Little et al., 1997; for a review, see Martinez-Gonzalez et al., 2017). This has led to over-prescription of antibiotics in many countries, including European countries (Neumark, Brudin, & Molstad, 2010; Tyrstrup et al., 2017), U.S.A. (Kronman, Zhou, & Mangione-Smith, 2014), or Australia (Fletcher-Lartey, Yee, Gaarslev, & Khan, 2016). Over-prescription contributes to an increase in antibiotic resistance (Friedman, Temkin, & Carmeli, 2016). Moreover, in the long term, the uptake of antibiotics may negatively impact children's future development and health conditions. For example, a positive association has been found between antibiotic prescription during infants' first six months of life and the development of asthma and allergy when they are six years old (Risnes, Belanger, Murk, & Bracken, 2011). Also, a positive association has been found between antibiotic prescription in the first six months of life and an increased probability of being overweight at seven years old among children whose mothers had an average healthy weight (Ajslev, Andersen, Gamborg, Sorensen, & Jess, 2011). Furthermore, antibiotics uptake increases the susceptibility to pathogens and is related to several health conditions such as inflammatory bowel disease, rheumatoid arthritis, type 1 diabetes, and atopy (for a review, see Francino, 2016).

Health outcomes and quality of life have also been associated with mother-infant attachment (Andrews, Meredith, & Strong, 2011; Feeney, 2000; P. J. Meredith & Strong, 2019). Humans are born predisposed to become attached to caregivers during their first year of life (Bowlby, 1969). When children develop trust in the availability and reliability of their attachment figures, their anxiety is reduced, and they can operate in the world with confidence (Bowlby, 1969).

Because not all relationships offer a secure base, infants use different strategies to address their attachment needs. Ainsworth et al. (M. D. Ainsworth, Blehar, Waters, & Wall, 1978) described infants' attachment organization in three attachment patterns: securely attached infants (named by Ainsworth as pattern B), avoidant infants (pattern A) and ambivalent infants (pattern C) (for a review, see Cassidy & Shaver, 2018). Securely attached infants (B) generally display their emotional communication and intentions openly by signaling or seeking contact with caregivers when distressed. They are easily comforted and use their caregiver as a secure base for exploration. Conversely, insecurely attached infants (A and C) do not rely on a secure base when distressed. Insecure-avoidant attached infants (A) tend to avoid proximity with their caregivers by over-activating the exploratory system, while insecure-ambivalent attached infants (C) are characterized by an ambivalent behavior, alternating between strong proximity seeking/contact maintenance and physical resistance to the contact with their attachment figures (DeWolff & van Ijzendoorn, 1997; Lucassen et al., 2011).

Parents of secure infants are highly sensitive, offering comfort and protection in alarming situations as is the case of infants' disease (M. D. S. Ainsworth, Bell, & Stayton, 1974). Maternal sensitivity has been defined by attachment theorists as mother's: (1) ability to read and interpret infant's solicitations and distress signals; (2) ability to comfort the infant in stressful situations; (3) ability to respond in a sensitive, contingent, and prompt way; and (4) availability to socially engage in a warm, reciprocal and contingent manner (M. D. S. Ainsworth et al., 1974; Beeghly, Fuertes, Liu, Delonis, & Tronick, 2011; Braungart-Rieker, Garwood, Powers, & Wang, 2001; Mesman, Oster, & Camras, 2012).

Attachment security has also been associated with health status, health visits, and symptom reporting (for a recent review, see P. J. Meredith & Strong, 2019). Secure attachment predicts better health and developmental outcomes when compared with insecure mother-infant relationships (P. J. Meredith & Strong, 2019) and seems to be associated with improved quality in the patient-doctor relationship (defined as patients` degree of trust and security evaluated in a self-reported measure) (Zaporowska-Stachowiak, Stachowiak, & Stachnik, 2019).

Inversely, an insecure attachment is more likely to be observed in children with chronic diseases (Cassibba, van Ijzendoorn, Bruno, & Coppola, 2004; P. J. Meredith &

Strong, 2019; Pietromonaco & Powers, 2015; Simmons, Goldberg, Washington, Fischerfay, & Maclusky, 1995). In a longitudinal study, it was found that insecurely attached infants had more somatic complaints at six years old (Lewis, Feiring, Mcguffog, & Jaskir, 1984).

However, insecure-avoidant and insecure-ambivalent individuals seem to adopt different responses to pain and sickness (McCallum & McKim, 1999; P. Meredith, Ownsworth, & Strong, 2008). Faced with the same symptoms, avoidant attached children and teenagers display higher levels of emotional control and lower levels of negativity compared with insecure-ambivalent individuals (Feeney, 2000). Furthermore, compared with secure attached, insecure-ambivalent individuals have higher symptom-reporting and request more health visits (Andrews et al., 2011; Feeney, 2000).

Since attachment patterns are behavioral strategies activated to overcome stressful situations, they are especially elicited when infants feel pain, fatigue, or sickness (Bowlby, 1969). In response, attachment figures need to find appropriate health-care and means to alleviate the infant's pain.

It is well documented that ambivalently attached infants tend to exaggerate the display of their emotions and needs in ways that influence attachment figures' behavior (Cassidy & Shaver, 2018). In the presence of any perceived danger (such as pain, hunger, fear, and others), these infants arouse their feelings of anxiety and despair to obtain responses from their attachment figures that can decrease the probability of imminent danger. This ambivalent pattern results from inconsistent, anxious, or absent caregiving (Beeghly et al., 2011; Cassidy & Shaver, 2018). To obtain responses and attention from their caregivers, ambivalent-attached infants react with over-emotional angry and fear responses expressed by heavy crying, inability to self-soothe or strong motor reactions (Barbosa, Beeghly, Moreira, Tronick, & Fuertes, 2018), alternating with behaviors of proximity seeking, contact and desire for comfort (M. D. S. Ainsworth et al., 1974; Bretherton, 1992). Therefore, we hypothesize that infants who exacerbate their emotions while feeling pain or physical illness (namely insecurely ambivalent attached infants) may raise exacerbated concerns to their parents and health professionals, eventually leading to antibiotic prescription.

However, other factors might contribute to antibiotics uptake, namely type of labor, breastfeeding, and enrollment in daycare. Regarding the type of labor, hundreds of bacterial species typically colonize human beings, and the infant intestinal colonization by microorganisms begins with oral inoculation by maternal vaginal microbiota (Houghteling & Walker, 2015; Jakobsson et al., 2014). A vaginal birth ensures that infants' body is colonized by the correct founding microbial species at birth, protecting them from infectious and non-infectious diseases (Buffie & Pamer, 2013; Rautava, 2016; Sassone-Corsi & Raffatellu, 2015). Breastfeeding is also an important factor for infants' health. The presence of secretory immunoglobin IgA in breast milk is important for the recognition of microorganisms of maternal origin, contributing to the establishment of the intestinal microbiota (Rautava & Walker, 2009). Moreover, many molecules present in breastmilk display antimicrobial activity as proteins κ-casein, α-lactalbumin, lactoferrin, haptocorrin, or the lysozyme enzyme that destroys the cell wall of gram-negative bacteria (Rautava & Walker, 2009). Therefore, breastfed children are less susceptible to infectious diseases. The age of infants when entering daycare may also be relevant given that some studies have reported a higher rate of infections in this context when compared with children reared at home (Schuez-Havupalo, Toivonen, Karppinen, Kaljonen, & Peltola, 2017).

To test the hypothesis that the prevalence of antibiotic uptake is higher in insecurely resistant attached infants compared with infants classified with other attachment patterns, we started by investigating the factors associated with infants' antibiotic consumption in the first nine months of life from a range of variables, including the type of labor (vaginal vs. non-vaginal), enrollment in daycare vs. reared at home, breastfeeding time-period (in months), quality of maternal interactive behavior (i.e., maternal sensitivity, maternal control, maternal unresponsivity), quality of infant's interactive behavior (i.e., infant's cooperative behavior, infant's compulsive behavior, infant's difficult behavior, infant's passive behavior), infants' clinical conditions at birth usually associated with increased health problems (gestational age at birth, gestational weight at birth, Apgar 1st minute, Apgar 5th minute), and socio-demographic variables, such as maternal age, maternal education, number of siblings, infant's gender. Moreover, we estimated the prevalence of infants' attachment pattern between those who consumed and those who did not consume antibiotics in the first nine months of life.

METHODS

Participants

The original sample comprised 176 mother-infant dyads. To homogenize our sample, a total of 42 dyads were excluded based on six exclusion criteria (Suppl. Inf. Fig. S1). First, dyads with mothers with less than seven years of formal education were not included. Second, dyads with babies not breastfed for, at least, the first month postpartum were also excluded. Third, dyads with infants who had severe or chronic health problems (e.g., asthma, cardiopathies) or allergies, were also excluded. The reason for excluding these dyads is that these health conditions could lead to more medical visits, eventually increasing the probability of antibiotic prescription. Additionally, infants with low birth and gestational age are more likely to present serious health and developmental conditions (for a review, see Fuertes et al., 2012). Therefore, we also excluded dyads with babies with low birth weight (BW) for their gestational age (GA) at birth (4th criterion); less than 32 weeks of GA (5th criterion); and less than 1500 g of BW (6th criterion). Ten of the excluded dyads presented more than one exclusion criterion.

The final sample comprised 134 mother-infant dyads, which included 57 girls and 77 boys and their respective mothers. The mean GA of the infants was 37.60 weeks (*SD* = 2.37 weeks) and an average BW of 2991.11 g (*SD* = 622.09 g). Ninety-seven infants were born full-term and healthy at delivery (≥ 37 and < 42 gestational weeks). The other 37 infants were healthy prematurely born (≥ 32 and < 36 gestational weeks). Infants were breastfed for an average of 3.91 months (*SD* = 2.60 months). Throughout the conduction of this study, all infants continued to be healthy (except for normal infections and other occasional minor diseases) and had normal development until our last observation at 12 months. Mothers were healthy at infants' birth and had no medical history (i.e., a clinical record) of chronic diseases, mental health disorders, or substance (alcohol/drug) abuse. Moreover, all mothers were married or living in cohabitation with the infant's father. All families were from low to high middle-class backgrounds, representing 75% of the Portuguese population (INE, 2011).

Measures

Medical History Interview. In this interview, a female research assistant queried mothers about how many times their infants were ill, and if antibiotics were used in the first nine months of life. All mothers had information regarding antibiotic prescription; however, only 97 mothers were able to describe how many times their infants were ill.

Maternal Sensitivity in Free Play Interaction. The quality of the mother-infant relationship, namely, maternal sensitivity was assessed during a 5-min unstructured mother-infant free-play interaction coded using the scale Child-Adult Relationship Experimental Index (CARE-Index) (Crittenden, 2003). According to the CARE-Index manual, maternal sensitivity is defined as any pattern of behavior that pleases the infant and increases the infant's comfort and attentiveness and reduces his/her distress and disengagement. The CARE-Index was used to score qualitative dimensions of infant-adult interaction during free play at the 9-months lab visit. The CARE-Index system assesses seven aspects of mother-infant interactive behavior: facial expressions, verbal expressions, position and body contact, affection, turn-taking contingencies, control, and choice of activity. Each adult and infant are evaluated separately in each of these seven dimensions of interactive behavior. The points for each dimension are added to yield seven scale scores, three adult independent scales, namely, Sensitivity, Control, and Unresponsiveness, and four infant independent scales, namely, Cooperative, Compliant-compulsive, Difficult, and Passive, behaviors (Crittenden, 2003). CARE-Index was scored by two trained coders that were blind against the study hypothesis. Intercoder reliability was evaluated by comparing the two coders' ratings using intraclass correlation coefficients (ICC) (Cicchetti, 1994). The obtained overall average ICCs (.81) showed a substantial strength of concordance (Landis & Koch, 1977).

Mother-Infant Attachment. At the 12-months visit, mother-infant dyads were videotaped during the Strange Situation (SS) (M. D. Ainsworth et al., 1978). SS is a 21-minute laboratory paradigm consisting of a sequence of eight episodes designed to place mild but increasing levels of stress on the infant (i.e., being introduced to an unfamiliar playroom, interacting with an unfamiliar adult stranger, and brief separations from and reunions with the mother). The videotapes of infants' attachment behavior during the SS were scored by two trained, reliable coders following the procedures developed by M. D. Ainsworth et al. (1978) and Main and Solomon (1990). Infants were classified as either securely attached (B), insecure-avoidant (A), and insecure-ambivalent (C). Cohen's kappa coefficient for attachment classifications among coders was .90, corresponding to an excellent agreement (Landis & Koch, 1977).

Procedures

Mother-infant dyads were recruited after delivery at hospitals of Santo Espirito da Ilha Terceira (Azores), S. João (Oporto), and Pedro Hispano (Matosinhos). Recruitment was authorized by the three hospitals' administration boards based on favorable reports of their respective ethical committees. Pregnancies had been monitored according to recognized obstetrical standards and mothers did not have major medical complications associated with delivery.

This study was performed according to the guidelines presented in the Declaration of Helsinki, the American Psychology Association (APA) guidelines for research, and the EU General Data Protection Regulation (GDPR) - Regulation (EU) 2016/679. No risks of vulnerability/stigmatization of the participants resulting from this research were expected and the methods and proceedings selected are extensively used in Developmental Psychology research over the last decades, without risks reported. All procedures involving human subjects in this study and the original projects (PTDC/ PSI-EDD/ 110682/ 2009; PTDC/ MHC-PED/ 1424/ 2014) were approved by the Ethics Committee of the Portuguese hospitals of Santo Espirito da Ilha Terceira (Azores), S. João (Oporto) and Pedro Hispano (Matosinhos), and the National Commission for Data Protection (2019/2017), and were developed in collaboration with the respective nursing and medical teams.

Under the protocols established with the Ethics Committees, potential participant mothers were contacted in the neonatal obstetric units within the first 48 hours after infants' birth. The study's purpose and procedures were then explained, and mothers were asked about their willingness to participate and if so, informed consent was collected (signed by the parents). Those who had shown interest in participating were administered a brief interview to collect demographic information. With the mothers' consent, data concerning infants' perinatal health status was abstracted from medical records. Demographic and health information was checked to determine eligibility. Procedures were followed to ensure the confidentiality of the data collected.

Mothers were recruited at the maternity ward (newborn's first 48 h of life period), and those who accepted to participate, were then re-contacted near the infants' age of 9 and 12 months to schedule the follow-up visits to the laboratory. At the 9-months visit, mothers described their infant health and development in the Medical History Interview and participated with their infant in the 5-min unstructured free play interaction. At the 12-month visit, dyads were videotaped in the Strange Situation (SS) paradigm (M. D. Ainsworth et al., 1978).

Data analyses

A total of six sets of statistical analyses were conducted to address the goals of the current study. First, we calculated the prevalence of antibiotic consumption until 9 months of life. Second, to study the factors associated with antibiotic uptake, we performed Student *t*-tests using the following variables: breastfeeding time-period, maternal sensitivity, maternal control, maternal unresponsivity, infant cooperative behavior, infant compulsive behavior, infant difficult behavior, infant passive behavior, Apgar 1st minute, Apgar 5th minute, GA, GW, maternal age, maternal education, and number of siblings. Third, Chi-Square tests were used to study the prevalence of antibiotic uptake according to the type of labor, enrollment in daycare, and infant's gender. Fourth, the factors significantly associated with antibiotic uptake in Student's *t*-test were computed in a binary logistic regression (forward stepwise – Wald) to explore the predictors of antibiotics consumption in the first 9-months of infants' life. Fifth, the distribution of infants' attachment pattern was analyzed using univariate frequency analysis. Sixth, a χ^2-test was used to study the prevalence of antibiotic consumption among patterns of attachment, followed by a z-post hoc analysis. Bonferroni correction was used for adjusting *p*-values .

To carry out the mean difference tests, the assumptions of normality and homogeneity of variances were tested. The significance level of $p < .05$ was assumed for analyses.

Data availability

Available at URL: https://osf.io/gqw2f

RESULTS

Factors associated with antibiotics uptake

At nine months of age, antibiotics had already been administered to 39.6% of infants in our sample. From a range of factors included in our analysis, only maternal sensitivity (*p* = .008), infant cooperative behavior (*p* = .014) and Apgar at 1st (*p* = .020) and 5th minute (*p* = .013) were associated with antibiotic uptake (Table 1). Maternal sensitivity and infant cooperative behavior were significantly higher in infants that did not consume antibiotics (Table 1). On the other hand, the mean Apgar, both at 1st and 5th minute, were significantly higher among infants who consumed antibiotics (Table 1). No mean differences were found for maternal age (*p* = .65), maternal education (*p* = .52), number of siblings (*p* = .23), breastfeeding time-period (in months) between infants who consumed and infants who did not consume antibiotics in the first nine months of life (*p* = .83) (Table 1).

Using binary logistic regression analysis, we tested the four significant variables from the above t-student analysis (maternal sensitivity, infant cooperative behavior, Apgar at 1st and 5th minute) and found that maternal sensitivity (*p* = .02) was negatively associated with antibiotics uptake (Table 2).

No significant differences were found according to type of labor ($\chi^2_{(1,134)}$ = .691; *p* = .406), enrollment in daycare ($\chi^2_{(1,134)}$ = 3.570; *p* = .059), nor according to infant gender ($\chi^2_{(1,134)}$ = .827; *p* = .363) and antibiotics uptake. In our study, 60.4% of infants born vaginally and 39.6% of infants born non-vaginally consumed antibiotics before completing 9-months. From the group of infants who attended daycare, 51.2% consumed antibiotics, and 34.1% of infants reared at home consumed antibiotics. The proportion of ambivalent-attached infants enrolled in daycare was 20.9% and of securely-attached infants was 53.5%. The only three ambivalent-attached infants, who consumed antibiotics, were attending daycare. Moreover, among infants reared at home, 90.4% (= 38/42) of secure-attached infants did not take antibiotics, which contrasts with 15.0% (= 3/20) of ambivalent-attached infants. Also, 35.1% of the girls and 42.9% of the boys consumed antibiotics.

Attachment patterns and antibiotics' uptake

Our sample comprised 29.8% of infants classified as insecure-avoidant attached, 48.5% classified as secure, and 21.6% classified as insecure-resistant. This level of security is lower than the mean among Western countries of 67% (van Ijzendoorn & Sagi-Schwartz, 2008). However, a literature systematic review has shown that attachment security varies between 45% and 65% in Portuguese samples (reviewed by Faria, Lopes-dos-Santos, & Fuertes, 2014).

When comparing mother-infant attachment classification between infants that used antibiotics with those that did not use antibiotics, we found that ambivalent-attached infants were more likely to have received these drugs than secure or avoidant attached infants ($\chi^2_{(1,134)} = 40.103$; $p < .001$; Table 3). Indeed, 89.7% (26/29) of infants classified as ambivalent in the Strange Situation at 12 months were treated with antibiotics in their first nine months of life, whereas only 32.5% (13/40) of avoidant and 21.5% (14/65) of securely attached infants have been treated with antibiotics in the same period (Table 3).

Given that there was no significant difference between secure and avoidant attachment patterns, we conducted further analyses combining both attachment groups ($\chi^2_{(1,134)}$ = 38.859; $p < .001$). Moreover, for children with insecure-ambivalent attachment, the odds of antibiotic consumption were 25.037 (95% confidence interval, 7.012-89.394) times higher than children with the other patterns of attachment (secure and avoidant attachment combined).

Discussion

This is the first study to explore a link between infant attachment and antibiotic prescription, as well as to study the factors associated with antibiotic prescription among a range of maternal and infant factors. From all variables included in this study, maternal sensitivity had the highest impact on antibiotic uptake until infants' nine months of age. The fact that a maternal variable is a crucial factor explaining antibiotic consumption, rather than others factors, including infant variables (e.g., breastfeeding, Apgar at 1st and 5th min, GA, or GW) or environmental conditions such as infants raising conditions and socio-demographic variables (e.g., maternal education, maternal age, number of siblings) is a striking result, particularly because those variables are usually related with infant´s health conditions or the likelihood of contagion by bacteria (Pettigrew et al., 2003; Thacker, Addiss, Goodman, Holloway, & Spencer, 1992;

Thompson, Monteagudo-Mere, Cadenae, Lampi, & Azcarate-Peril, 2015). In line with our results, past research has shown that mothers with a high score in the sensitivity scales tend to be highly sensitive in comforting and caring for their infants when ill (Belsky, 1999; DeWolff & van Ijzendoorn, 1997; Lucassen et al., 2011). In general, these mothers are better at interpreting infant's needs and cues, eventually giving a prompt response in case of a disease, and attenuating symptoms and somatization (for a review, see P. J. Meredith & Strong, 2019).

Less sensitive mothers tend to be more anxious and to have more negative perceptions of their infants' health condition (McCallum & McKim, 1999). We speculate that these mothers described their infants' symptoms less precisely (e.g., reporting more days of fever), leading physicians to believe that infants had a bacterial disease. Moreover, physicians may perceive maternal expectations for an antibiotic prescription. This relates to another study that found that physicians' perception of parental expectations of antibiotic prescription (i.e., the physicians perceived parental pressure for antibiotic prescription) was the only significant predictor of antimicrobials prescription in conditions of presumed viral etiology (Mangione-Smith, McGlynn, Elliott, Krogstad, & Brook, 1999). In sum, possibly, maternal behavior affects the likelihood of antibiotic prescription.

Attending a daycare is usually associated with increased contagion rates. For example, in a literature review, Thacker et al (1992) have shown that the risk of some infectious diseases was at least two times higher among children attending daycare than among infants reared at home (Thacker et al., 1992); see also refs. (Pettigrew et al., 2003; Thompson et al., 2015). However, in our study, the proportion of infants consuming antibiotics is slightly lower among those attending a daycare than among those reared at home. Yet, the only three ambivalent infants that did not take antibiotics were not attending daycare, which does not support the thesis that other family and educational contexts can buffer the social-emotional effect of insecure attachment (Biringen et al., 2012). Nevertheless, this result should be taken with caution taking into consideration that this was observed in only a few cases.

We further investigated the link between infant attachment patterns and antibiotic consumption. As hypothesized, our results show that the prevalence of antibiotic consumption until 9-months of age is significantly higher in insecure-ambivalent attached infants than among other infants. Indeed, ambivalent-attached infants tend to react to stressful events and pain with overwhelmed and angry behaviors while resisting mothers' attempts to soothe their distress (Mills-Koonce, Propper, & Barnett, 2012). These reactions are expected in the presence of health problems, leaving parents overconcerned, and feeling helpless in responding to their infants' needs (Feeney & Ryan, 1994; Scher & Mayseless, 2000). Pressing doctors to prescribe antibiotics can be a result of the parents' sense of helplessness. Indeed, it is known that facing parents' lack of effectiveness, infants become distrustful and uncertain that their parents serve as a secure-base (McElwain & Booth-LaForce, 2006). According to attachment theory, these experiences and expectations (*secure based scripts*) are internalized in infants' working attachment models, thereby affecting infants' emotional development (Barbosa, Beeghly, Moreira, Tronick, & Fuertes, 2020; Beebe et al., 2010; Bowlby, 1969). The lack of sense of trust and of the ability to rely on others generated by early interactions lead to emotional regulatory problems, unbalanced social information processing, lack of resilience in relationships, and emotional maladjustment (e.g., Belsky, Friedman, & Hsieh, 2001; Cassidy, 1994; Elicker, Englund, & Sroufe, 1992; Greenberg, Speltz, & Deklyen, 1993; Kochanska, Barry, Stellern, & O'Bleness, 2009).

The associations between antibiotic consumption and the development of later diseases (Ajslev et al., 2011; Francino, 2016; Risnes et al., 2011), as well as the risk of increased antibiotic resistance (Friedman et al., 2016), have concerned microbiologists, epidemiologists, and health practitioners in general. In the present study, 39.6% of the infants had already consumed antibiotics before completing nine months of life, which agrees with another study showing that 54% of Portuguese infants consumed antibiotics in the first 12 months of life (ISAAC, 2011).

Antibiotic uptake has also been associated with mental problems, most likely through microbiota disruption (Francino, 2016). For example, it was recently shown that the microbiota of people with depression was depleted of the same two bacterial species (Valles-Colomer et al., 2019). Although performed with adults, that study suggests that antibiotics may also impact infants’ behavior. It could be argued that our study does not rule out the alternative hypothesis that infants became insecurely attached due to antibiotic uptake That is, the uptake of antibiotics during the first nine months of life could have triggered a cascade of physiological and regulatory processes contributing for an insecure-ambivalent pattern when infants completed 12 months.

Contrary to this hypothesis, it was maternal sensitivity that had the highest association with antibiotic uptake. On the other hand, the infant cooperativity is also associated with antibiotic uptake, a variable that is related to maternal sensitivity (Crittenden & Bonvillian, 1984; Fuertes, Faria, Soares, & Crittenden, 2008). It is, therefore, our opinion that the causal connection between these variables must be further investigated.

Finding that antibiotics are prescribed more often to insecure-attached infants than to infants classified otherwise, may be viewed with some concern, and needs further research. Even when we replicated the analysis with a more heterogeneous sample (with the original sample of 176 mother-infant dyads), which includes, for example, preterms, or infants with chronic diseases, analogous results are obtained (Supplementary Information Table S1 and S2). Futures studies should include qualitative and phenomenological research to gather more and deeper information regarding maternal representations about antibiotics efficacy and drawbacks, doctor-patient relationship, and mothers' role as caregivers when their infants are ill.

Regarding intervention, health services must improve communication with parents, explaining to them both that antibiotics are both advantageous and disadvantageous. Moreover, our results reinforce the need to enhance doctor-family relationships based on open and empathic communication focused on responding to parents' concerns (Becker, Lin, & Miller, 2018). Based on prior research (Bakermans-Kranenburg, van IJzendoorn, & Juffer, 2003), to prevent attachment insecurity and their consequences on infants' and parents' behavior, a family-centered approach (as, for example, The Circle of Security) can help moderate infant and parental stress levels (Palermo & Chambers, 2005).

Limitations, strengths, and future directions

The present study has both limitations and strengths that should be considered when evaluating the results. One limitation is that the current sample of Portuguese mother-infant dyads was mostly from low-risk socioeconomic backgrounds and homogeneous in race/ethnicity Thus, our findings may not generalize to mother-infant dyads in other ethnic/racial groups, geographic locations, and may not characterize infants' social interactions with other caregivers such as fathers or extended family members. A third limitation is the relatively small sample size (N = 134), which may have limited statistical power. Replication of the current study in larger, more diverse samples and included fathers is needed. The primary strengths of the current study include its prospective, longitudinal measures (at 9 and 12 months), the inclusion of a well-described observational paradigm (Strange Situation) and free play observations, and the use of detailed behavioral coding systems.

It may be helpful to learn more about maternal reactions and anxiety especially when their infants are ill (McClure, Brennan, Hammen, & Le Brocque, 2001; Stevenson-Hinde, Shouldice, & Chicot, 2011; Whaley, Pinto, & Sigman, 1999). Although we assessed maternal interactive behavior, maternal anxiety was not directly assessed in our study and we believe that this can be an important aspect to investigate in future studies (McElwain & Booth-LaForce, 2006). Infants' health problems during the first nine months of life may trigger a cascade of reactions, and the measurement of maternal anxiety could help us to understand the impact of ambivalent attachment behavior on their mothers. According to Sameroff and Fiese`s Transactional Model (Sameroff & Fiese, 2000), it is likely that, in face of infants' expression of pain and discomfort, parental stress increases and contributes to raising, even more, infant physiological and behavioral responses (Boyce & Ellis, 2005; Propper & Moore, 2006). This reciprocal process should be studied in the future.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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Table 1 | T-test for mean differences of infant and maternal factors according to antibiotics consumption

	Uptake of antibiotics			No uptake of antibs.				
	Mean	*(SD)*	*N*	*Mean*	*(SD)*	*N*	*t*	*p*
Breastfeeding (in months)	3.85	2.60	53	3.95	2.60	81	.811	.826
Maternal sensitivity	7.09	2.19	46	8.22	2.30	74	2.697	.008
Maternal control	4.59	2.95	46	3.61	2.92	74	1.775	.079
Maternal unresponsivity	2.26	2.74	46	2.16	2.39	74	.209	.840
Infant cooperative behavior	7.11	2.38	46	8.20	2.21	74	2.518	.014
Infant compulsive behavior	2.72	3.27	46	1.61	2.81	74	1.905	.060
Infant difficult behavior	2.63	2.85	46	2.20	2.66	74	.820	.414
Infant passive behavior	1.89	2.11	47	1.93	2.00	74	.101	.920
Gestational Age	37.68	2.27	53	37.54	2.44	81	.337	.737
Gestational Weight	2911.42	574.67	53	3043.26	649.43	81	1.233	.220
Apgar 1st minute	8.87	.44	52	8.50	1.22	74	2.365	.020
Apgar 5th minute	9.88	.32	52	9.59	.93	76	2.537	.013
Maternal age	30.51	5.14	53	30.09	5.31	81	.459	.647
Maternal education	13.38	3.48	53	13.79	3.84	81	.645	.520
Number of siblings	.87	.79	53	1.05	.93	81	1.212	.228

Table 2 | Summary of binary logistic regression analyses predicting antibiotic's uptake

	B	*S.E.*	*Wald*	*Exp(B)*	*95% C.I. for Exp(B)*		*p*
					Inferior	*Superior*	
DV: Antibiotic's uptake							
Maternal sensitivity	-.210	.090	5.421	.811	.680	.967	.020
Constant	1.167	.701	2.768	3.211			0.096

Table 3 | Frequency of attachment patterns at 12 months according to antibiotic uptake until 9 months.

	Attachment at 12-months			Total
	Avoidant (A)	Secure (B)	Ambivalent (C)	
Frequency of infants that did not take antibiotics (%)	27 (33.3%)[a]	51 (63.0%)[a]	3 (3,7%)[b]	81
Adjusted residuals	1.1	4.1	-6.2	
Frequency of infants that took antibiotics (%)	13 (24,5%)[a]	14 (26,4%)[a]	26 (49.1%)[b]	53
Adjusted residuals	-1.1	-4.1	6.2	
Total	40	65	29	134

Note: Pearson Chi-Square = 40.103, DF = 2, p< .001. Each superscript letter denotes a subset of Attachment at 12-months categories whose column proportions do not differ significantly from each other; p< .05 (column proportions test with Bonferroni adjustment).

Supplementary Figure S1:

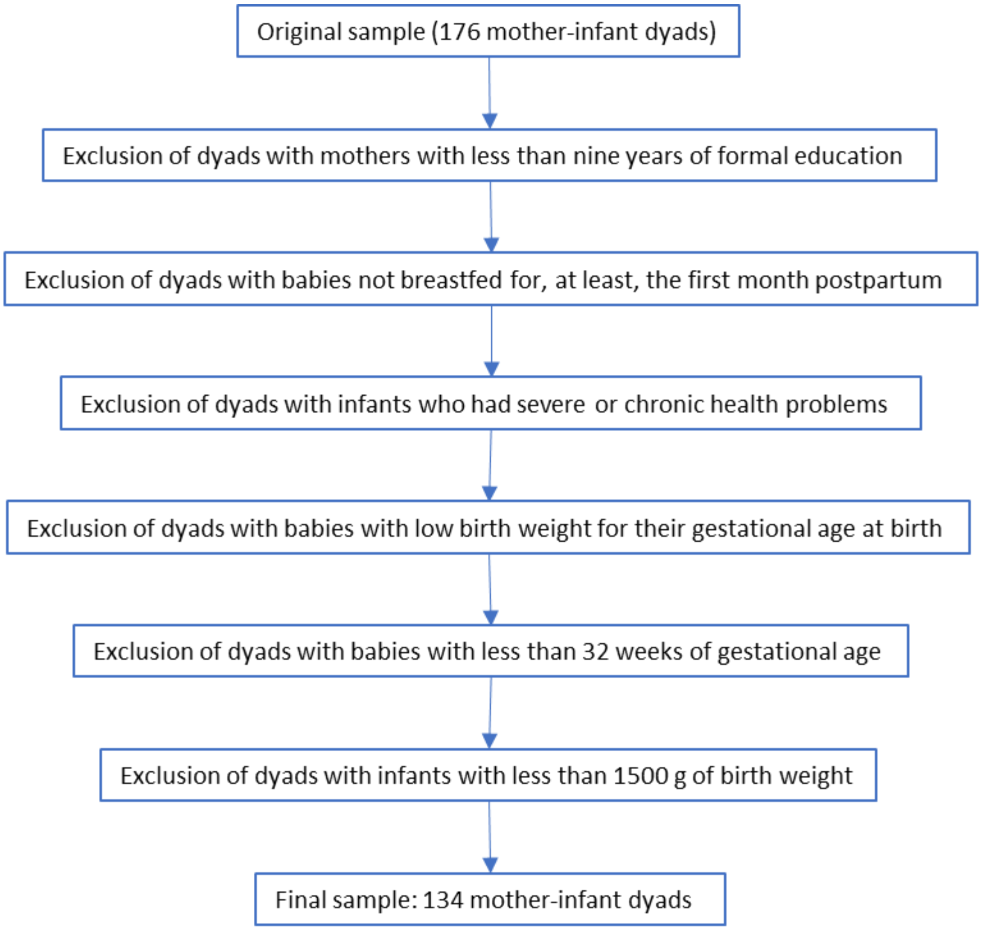

Figure S1: Flow chart of exclusion of participants. Ten dyads had more than one exclusion criterion. See main text for a detailed explanation of each criterion.

Supplementary Table S1| T-test for mean differences of infant and maternal factors according to antibiotics consumption

	Uptake of antibiotics			No uptake of antibiotics				
	N	*Mean*	*SD*	*N*	*Mean*	*SD*	*t*	*p*
Breastfeeding (in months)	76	3.88	2.57	97	3.85	2.55	.093	.926
Maternal sensitivity	68	6.93	2.45	92	8.11	2.35	3.091	.002
Maternal control	68	4.26	3.05	92	3.89	2.97	.778	.438
Maternal unresponsivity	68	2.85	3.09	92	2.05	2.33	1.865	.064
Infant cooperative Behavior	68	6.84	2.62	92	8.03	2.30	3.062	.003
Infant compulsive behavior	68	2.88	3.51	92	1.85	2.98	2.012	.046
Infant difficult behavior	68	2.47	2.91	92	2.10	2.56	.859	.392
Infant passive behavior	68	1.72	2.57	92	2.08	2.03	.976	.331
Gestational Age	76	37.17	2.69	100	37.31	2.60	.359	.720
Gestational Weight	76	2750.86	701.48	99	2956.35	697.05	1.926	.056
Apgar 1st minute	75	8.64	1.04	92	8.43	1.18	1.181	.239
Apgar 5th minute	75	9.76	.53	94	9.57	.86	1.400	.163
Maternal age	76	30.79	5.23	100	29.47	5.41	1.625	.105
Maternal education	76	11.54	5.05	100	12.30	4.72	1.018	.310
Number of siblings	76	.88	.80	100	.99	.94	.803	.423

Supplementary Table S2 | | Frequency of attachment patterns at 12 months according to antibiotic uptake until 9 months with the original sample.

	Attachment at 12-months			Total
	Avoidant (A)	Secure (B)	Ambivalent (C)	
Frequency of infants that did not take antibiotics (%)	34 (63.0%)[a]	61 (77.2%)[a]	5 (11.6%)[b]	100
Adjusted residuals	1.1	4.9	-6.9	
Frequency of infants that took antibiotics (%)	20 (37.0%)[a]	18 (22.8%)[a]	38 (88.4%)[b]	76
Adjusted residuals	-1.1	-4.9	6.9	
Total	54	79	43	176

Note: Pearson Chi-Square = 50.018, DF = 2, $p < .001$. Each superscript letter denotes a subset of Attachment at 12-months categories whose column proportions do not differ significantly from each other; $p < .05$ (column proportions test with Bonferroni adjustment).